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Scientific Clinical Validation Of Siddha Drug Ayabirungarajakarpam For Iron Defeciency Anemia: Single Arm Non-Randomized Study

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Abstract*: The main focus of this study is to provide scientific validation ofAyabirungarajakarpam(ABK), a herbo-metallic synergistic Siddha formulation which is commonly used as anti-anemic drug. The herbal formulations have been the source of treatment of anemia before the invention of synthetic medicines because the diseases are born with human and drug came in to existence since a very early period to relieve people from their ailments. The traditional medicine which is in use from the time immemorial are found to be derived from natural sources because of remarkable therapeutic effects and less side effects. The 116 Iron deficiency anemic(IDA) patients both sex with age limit range of 19-60 with the typical clinical signs of IDA and the Hb within the range of 7-11gm/dl were enrolled after obtaining written consent.The patients were asked to attend the OPD once in fifteen days to collect the medicines as well as to assess the physical complain. The laboratory investigation was performed three times 0th, 48th, 90th day during the course of study. The trial drug Ayabirungarajakarpam 500mg with lime juice twice a day was given for 48 days and then the patients were asked to attend the OPD 72th day to assess the clinical signs and 90th day to assess clinical signs as well as the laboratory investigation..The patients treated with ABK has got relief more than 90% for all the signs and symptoms reported here and well as significant increased in Hb, RBC,PCV, haematological indices and improvement of peripheral blood smear indicate the potency of ABK in reducing symptoms and haematinic activity. No any treatment related side effects have been reported during the course of study. Hence, ABK can be claimed as safe drug for oral therapy in human for the management of IDA.***

Keywords: Anemia, , blood smear, Ayabirungarajakarpam, Poverty, Paandu

1. INTRODUCTION

Anemia is a paramount public health problem affecting developed and developing countries with major consequences for human health as well as social and economic development. Iron deficiency identified as ten most serious risks in countries with high infant mortality complies with high adult mortality. Most of the adolescents are suffering from iron deficiency with its adverse effects on health and physical stamina because the functional consequences are known to occur prior to onset of clinical stage [1].The biological element iron plays the role in several cellular metabolic functions which is essential for the synthesis of haemoglobin which carries oxygen to the body's cells and transport carbon dioxide to the lungs. Stipulated regulation should be adopted to avoid iron deficiency or iron overload since the iron is toxic when present in excessive amount [2].

Iron deficiency (ID) is the most serious global nutritional deficiency. Physiologically, the stages of iron in the body as functional and storage iron while the depletion of iron from the storage is called "Iron deficient" while few noticeable outcomes may develops like reduce work capacity in regards to the tolerance, the depletion in progress and the Hb level fall below the normal range, the iron deficient become iron deficiency anemia. Anemia occurs when the total number of erythrocytes and or amount of haemoglobin is reduced. The state of

clinical condition that reduced haemoglobin level below the normal range norma of 130g/l in male and female 120g/l.[3] This resulting in deficient transport activity of oxygen and carbon dioxide to cater the physiologic needs which may vary to gender, age, altitude, pregnancy and smoking .but globally the most popular type of anemia with iron deficiency, the late stage of relatively long process in down turn of iron stores anemic will develop and functional consequences are known to occur prior to onset of clinical stage of ID[4]. Iron deficiency may develop at any stages of life , but is more widespread among pregnant women, young children and the endanger group identified as also the adolescent girls because of periodical blood loss during menstruation and simultaneously the iron requirement are at peak to meet their growing healthy physical stamina[5].

The siddha diagnosis is according to the perspective of biological humours and the treatment also aimed at the restoration of equilibrium of three humours with the help of taste. The six taste namely sweet (Earth& water),sour(Earth & Fire),bitter(Air and space),pungent(Air & fire),salt(Water& Fire) astringent(Earth & Air) are formed with selective integration of these pentad fundamental blocks of nature(panchabhutham)[6]. . Environment (season) and food play major role in the homeostasis of body functions. The essence of this concept indicated as "Food is medicine and Medicine is food" [7]. Food is very essential need for all in the world and also this is the prime contributing factor for iron deficiency (ID) due to poor nutritional value dietary intake or insufficient absorption [8]. Nearly, 50% cases of anemia are caused by ID [9]. Consumption of green leaves and fruits contribute to the intake of vitamin and mineral and biological elements like iron. The two forms of iron such as heme iron(organic) and non-heme iron(inorganic) are in food. Heme iron is well absorbable and derived from mostly flesh, fish etc since the heme iron is digested by pancreatic enzymes which make globin free molecule in the intestinal lumen [10].

Iron deficiency anaemia may disturb the secretion and functions of brain hormones specially the monoamine oxidase system. This may lead to impaired cognitive performance and dysfunctions of central nervous sysem.IDA among children has been demonstrated in many studies to be associated with cognitive and intellectual performance, motor development, coordination ,language development and scholastic achievements. Thus, adversely alter the body's immune system and decreased work capacity in adults which affect the GDP of the country [11]. The modern medicine concern oral iron supplements are available in the form of tablet and elixir. These are ferrous sulphate, ferrous fumarate and ferrous gluconate. Extended release carbonyl iron and polysaccharide iron complex formulations are available which are equally tolerated and effective[12]. The modern or Ayurveda & Siddha treatment are used extensively with several strategy in the prevention of IDA .Anyhow, the modern medicine treatment caused several side effect along with therapeutic untoward effect like heartburn, nausea, upper gastric discomfort, constipation, black stool,diarrhoea[13], whereas siddha &ayurvedic treatment is reported to be comparatively safer and free from side effect.

In my study, I have selected an important herbo metallic synergistic siddha drug Ayabirungarajakarpam(ABK) for paandu-anemia which consist powder of Iron(*ayam*), ore of iron(*Mandooram),* Wedeliachinensis(*birungarajam*), citrus limon(*Elumichchai)* and an attempt has been made to understand the role of ABK for anemia with special reference to the iron deficiency anemia (IDA) since it is the most common prevalent among world population and also considering the pathology and symptoms the iron contains trial drug will recover from this pathology and relief signs and symptoms as well as since ABK is a rejuvenating tonic will regulate metabolism properly and thus strengthen the body and immunity. Hence it will open a new avenue for the treatment of IDA along with preventive care since it is a natural Siddha formulation.

2. MATERIALS AND METHOD

Study design

Interventional Single arm, non-randomized in human subjects.

Study population

Assuming 10% loss of follow up the minimal sample size considered as 116 as per the single arm study sample size calculation [14].

Ethical concern

The clinical study protocol was approved by Ethical review committee, faculty of Medicine & Allied sciences, Rajarata University of Sri Lanka(ERC/2017/56),dated on 26th June 2018.

Trial Registration

The clinical trial was registered in Sri Lanka Clinical Trial Registry (SLCTR/2018/035) dated 29th October 2018.

Informed consent

The patients were informed the participation in this study is voluntary, free from any influence and have the choice to participate or withdraw from the study at any time. There will be no loss of medical care or any other available treatment for your illness or condition to which you are otherwise entitled. If you decide not to participate or withdraw from the study you may do so at any time. Participant was given seven calendar of days to make decision. Then after the consent form was issued to the patients in their own language and get it signed.

Selection of Patients and Method of Study

Inclusion criteria

- The subjects having cardinal clinical features
- Hb%- of11gm/dl -7gm/dl
- Serum ferritin<12mcg/l
- Age 19-60 years.
- Both sex

Exclusion criteria

- Hb% below 7gm/dl.
- Serum ferritin below 8mcg/l
- Any other type of Anemia except IDA
- IDA with any other complication like Cardiac diseases, Renal diseases, Liver disorder, Diabetes Mellitus, Hypertension,Thalasemiaminor, Bleeding disorders, Haemoglobinopathies and defective absorption like patients of Gastrectomy, Gastrojejunostomy etc.
- Pregnant mothers
- Lactating mother

In the phase of Screening and Enrolment of subjects about 130 patients were subjected to screen with the fulfilment selection criteria for the enrolment. Detailed history was taken from each patients including history of present illness, past illness, Socio-economic history, History of blood loss, history of Obstetric & gynaecological and menstrual history, Eating habit, quality and quantity of diet consuming, history of blood transfusion or donation and worm infestation. The physical examination was performed with special care of haemopoieticsystem,i.e.pallor,koilonochia,lymphadenopathy,hepatomegaly, splenomegaly, purpurea, bruises,pelvic examination in females, rectal examination and systemic

examination were performed on each patients. Blood test was carried out on 5ml venous blood by co-investigator, for Hb, Blood picture, haematological indices and serum ferritin in base line, after therapy and observational stage. Hb% and serum ferritin level was performed by Cyanomethoglobin method and ELISA kit respectively.
The pilot study with sample size 20 was conducted for one month before starting the study. The total number of total 130 patents having classical signs of anemia along with laboratory investigations confirmed and after adopting exclusion and inclusion criteria. Among 130 subjects, 116 Iron deficiency anemic patients both sex with age limit range of 19-60 with the typical clinical signs of IDA and the Hb within the range of 7-11gm/dl were enrolled after obtaining written consent. Out of 116 patients 102 were participated and have completed the study successfully. The study was set at MOH, Kuchaveli, Trincomalee and Teaching Hospital of Siddha medicine, Konesapuri,Trincomalee, SriLanka.

Discontinuation criteria

During the course of treatment patients can discontinue from the study for these reasons such as blood Hb% becomes less than 6gm/dl,any other acute illnesses,any severe untoward effect, unwillingness to continue, in adequate response to treatment,problem with compliance of trial iron supplement. Participants can withdraw from the study by informing to principle investigator [15].

Method of study

The patients were asked to attend the OPD once in fifteen days to collect the medicines as well as to assess the physical complain. The laboratory investigation was performed three times 0^{th}, 48^{th}, 90^{th} day during the course of study. The trial drug Ayabirungarajakarpam 500mg with lime juice twice a day was given for 48 days and then the patients were asked to attend the OPD 72^{th} day to assess the clinical signs and 90^{th} day to assess clinical signs as well as the laboratory investigation. The patients did not allow continuing the treatment who failed to collect the drug in a stipulated period.

Assessment Criteria

The results of the clinical study will be assessed on the basis of the observations of clinical features and laboratory findings. Assessment will be done by considering change in the subjective as well as the objective parameters in baseline, during therapy, end of therapy and post therapy. The patients will be assessed every 14 days for recording the improvement clinical and biochemical parameters for one mandalam(48 days) and 6 weeks for post therapeutic follow up. The subjective parameters will be assessed based on the scoring of health wellness and quality of life questionnaire [16].

- Subjective parameters – Signs and symptoms of anemia such as fatigue, palpitation, dyspnoea, pallor
- Objective parameters – Hb, RBC, HCt, MCV, MCH, MCHC ,Serum ferritin

Overall assessment criteria of results

The total effect of the total effect of therapy will be assessed as follows:
Complete remission 100% relief will be considered as complete remission.
Very good improvement -76%-99%
Good improvement -51-75%
Fair improvement -25-50%
Poor improvement - >25%

Data storage and Participant Log

A log with the patients name and date of birth will be kept along with their unique study number in a separate file. All the data generated from the study will be stored in an anonymous form in a bespoke data base which will also be password protected. Participant only be identifiable by their study number, all paper work will be kept in a locked filing cabinet in a locked office.

Participant Log Keep an electronic log of participants, who fulfil the eligibility criteria, subjects who are invited to participate in the study, subjects who recruited and leave the trial. Reasons for non- recruitment (e.g.; non-eligibility, refusal, administrative error) will also be recorded. I will attempt to collect to reasons for non-participant from subjects who decline to take part after previously providing contact details. During the study will document reason for withdrawal from the study and loss to follow up [17].

Selection and Intervention of trial drug

ABK is a herbometallic formulation quoted in text of "Siddha vaithiyathirattu", as selected as test drug. The final powdered compound was modified into capsule form to enhance the palatability and for easy administration. De-worming was done before therapy.Patient will be given 1 capsule 500mg of ABK twice a day with 200ml lime juice as supplementary therapy (Anupanam) after meal for one mandalam(48days). Further 6 weeks will be the follow up period. De-worming will be done before therapy, case registration for the study from the OPD.The participant will be asked to report every two weeks up to further six weeks to the research study to assess subjective and objective parameter[18].

Schedule of Treatment

- Nature of Trial drug –Powder
- Form of Trial drug – Capsule
- Dose of the Trial drug -500mg/bd/day
- Route of administration --Oral
- Vehicle(Anupanam) of trial drug –lime juice
- Duration of therapy –One Mandalam-48 days
- Follow up –every 2 weeks
- Post therapeutic observation period -42 days
- Follow up – Every two weeks
- Total evaluation period – 3months
- Diet – Normal diet was advised

Adverse events

To monitor safety, tolerability and sudden adverse effect of trial, the subjects were assessed clinically (history) and biochemically during the course of the study. Participant was instructed to contact Principal investigator at any time after consenting to join the trial, if they have an event that requires hospitalization or an event that result in persistent or significant disability or in capacity.Any serious adverse events that occur after joining the trial will be reported in detail in the participant's medical notes, Common side effect of iron therapy will be addressed as minor adverse events such as Constipation, Black stool, diarrhoea, heart burn, nausea, and abdominal pain. The adverse effect of trial drug, the clinical criteria were adopted and documented in adverse effect evaluation format during the course of study. This will be graded based on CTCAE grading score as follows [19].

Adverse event evaluation criteria

- To rule out possible adverse effect of trial drug, clinical and biochemical criteria will be adopted during the study and follow up period.

- G 1 –Mild, asymptomatic, clinical or diagnostic observation only; intervention not indicated.
- G2 - Moderate, minimal local or non invasive, intervention indicated, limiting age appropriate.
- G 3 – Severe or medical significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated,disabling;limiting self-care ADL.
- G 4- Life threatening; consequences, urgent intervention indicated.
- G 5 – Death related to AE

Statistical analysis of data

The assessment of objective parameters paired "t" test was adopted and software used for paired t test was sigma state 3.5(SSI,501, Richmon,CA).

Outcome

- **Primary outcome**

The amount of Hb% gm/dl gain per month will be considered as primary outcome of this trial since the laboratory investigation as objective parameter than patient's impression of clinical features.

- **Secondary outcome**

Decrease the degree of cardinal signs of Iron deficiency anemia as well as side effect and tolerability will be recorded as per the criteria of adverse event assessment.

3. RESULTS AND DISCUSSION

New drug discovery process can be done through the systematic examination of published formulations which assist us to invent a safe and synergistic formulation [20]. The therapeutic effective plants have shown the importance since their market for herbal drugs has grown at an attractive rate due to a global revival in alternative medical health care system [21]. However Modern allopathic medicine has its root in ancient medicine but the encumbrance of developing herbal medicine are lack of scientific documentation, biopiracy, biodiversity, over exploitation and infrastructure [22]. There is growing evidence to show that old molecules are finding new applications through a better understanding of conventional knowledge and clinical observation. Therefore, the conventional knowledge, modern medicine, and biomedical sciences form the triangle to invent innovative newer, safer, cost effective and efficacious formulations [23].

There were two peak of iron deficiency anemia 19-40 years and 41-60 years affected 75.4% and 24.5% respectively. In this study 72 patients were found to have anemia due to multiple factors like dietary deficiency, worm infestation and poor socio-economic status. In the 19 patients due to chronic blood loss and the remaining11 patients could not find significant defined causes. The majority of the female were aged between 19-60 years (64.7%).In ill-literate peoples the poor awareness about the nutritional diet, negligence towards the disease and poor economical condition are the rationale for the high incidence of anemia. The inadequate dietary supplements, frequency of give birth are the reasons among poor and middle class. In this study, the considerable percentage of the patients 59% were either the labours or house hold workers, they were not economically rich to meet their dietary needs and also could not pay much attention in their health.

ID is seen more frequently those who are vegans. The vegetarian diet bioavailability is 10%, while it is 18% in non-veg diet with vegetables as per the estimation food and nutrition board, United States[24]. Vitamin A is needed for mobilizing the iron from its storage site. In vitamin A deficiency, even though the iron store is normal but Hb is low while stored iron

cannot be used, as a result ID occurs.The non-vegetarian foods such as meat, fish etc contain high amount of heme iron which facilitate the absorption with high bioavailability. In the present study majority of the patients were reported to consume mixed diets but take non-vegetarian foods occasionally.

Subjective parameter (symptoms & signs)

The patients registered with various signs and symptoms but the incidence of classical signs andsymptoms weakness(100%),Fatigue(88%),palpitation(91%),pallor(80%),effort intolerance(78%),breathlessness(75%),pedal odema(44%) cases were found. Other symptoms like heartburn,constipation and excessive sleep were the very occasional complains. Data was analysis by independent t-test using SPSS, *statistically significant (P>0.05) comparing two groups Before and After Treatment(BT and AT), significant level alpha 0.05 for two-tilled.

The maximum number of patients 64% female belongs to age group 19-40 years.68.6% from rural area and 58.8% from middle socio economic status. The signs and symptoms of IDA showed statistically significant improvement for the ABK therapy. (Table 2 and Fig 1).The weakness 98.23%,palpitation 97.14%,pallor 90.58%,fatigue 95.62%, breathlessness 96.89%,Effort intolerance 93.23%,pedal odema 90.16%.

The symptoms like fatigue and weakness are due to decreased red cell production and decreased haemoglobin resulting deficient in nutritional enrichment to the tissues. The effect of therapy the two symptoms showed significant results with the ‘p’ value 0.000 in reducing weakness and fatigue. The patients feel breathlessness on exertion, due to decreased blood (*Senneer*) quality while Hb fails to carry out oxygen to the body. The marked improvement after ABK therapy indicates the drug has the potency to increase the blood quality and is effective to control this symptom. Low Hb percentage dilutes the blood which results in fall of intravascular osmotic pressure as the fluid from lower to higher osmotic pressure in the body, intravascular fluid exudates into the extra-vascular tissue spaces specially in the dependant part of the body producing pedal odema. The test drug increase the Hb percentage and causes rise in osmotic pressure inside the capillaries. This resulting in return of extra vascular fluid into the blood vessels and subsequent decrease in pedal odema.

In Siddha medicine,*paandu* is considered as *pithadosha* disease when *pitha* dominant, *vatham* vitiates blood(*senneer*) leading to affect the strength and complexion of the body, followed by imbalance in the remaining six body elements (*Udalkattukkal*). consuming *Pitha* aggaravating diets which contain mainly sour,salt and pungent taste vitiates *dhathu* by increasingpithadosham leading to anemia. In the etiopathogenesis according to siddha, the involvement of body elements(dhathus), specially the Intestitial fluid(rasa dhathu) causes depletion of nutrients and subsequently malnourishment to other dhathus and causes imbalance of blood(*senneer*) and immunity(ojas) and thus produce weakness of body, lethargy, pallor, palpitation, dyspnoea etc.

Pallor is the most important presenting sign of anemia. The *pirajaka and Ranjaka pitham* were affected on the appearance of pallor sign. The effect of therapy the sign pallor showed significant results with the ’p’ value 0.000 in reducing pallor. This may be due to improve the status of *ranjakapitham* and *pirajakapitham* by maintaining the quality of blood. The palpitation may develop due to lack of proper nourishment to the tissues when blood (Senneer) quality was affected. This leads to again defect in oxygen carrying capacity all over the body tissues especially to the heart. In this circumstances the heart has to pump forcibly to pump the blood to compensate this mechanism while patients may feel their heart beat. The effect of ABK therapy the sign palpitation showed significant results with the ‘p’ value 0.000 in reducing palpitation.

Objective parameter analysis

Haematology parameters such as Hb, RBC, PCV. MCV, MCH,MCHC, PBS and biochemical parameter serum ferritin were analysed before and after treatment with the trial drug ABK and were given in the table 3. The following changes have been noticed on analysing the statistical data regarding the haematological parameter. The Hb has increased (.11 ± 1.00 $p<0.05$) during the course of treatment with ABK for 48 days (one mandalam) and (12.03 ± 1.08 $p<0.05$) also has increased during the non drug therapy period for other 42 days. Over all statistically significant increase2.72g/dl (12.03-9.31,$p<0.05$) has been noticed in the 3 months of period. Similarly, RBC,PCV, MCV,MCH,MCHC, SERUM FERITIN has also been increased significantly.(Table 4).The peripheral blood smear revealed improved 81.37%.from MCHC,NCHC,MCNC in before and after treatment with ABK become NCNC(Table 5).Lauha(Iron),Mandoor(iron oxide are the traditional metallic raw materials which are used in the preparation of Lauhabhasma(incinerated iron),Madoorbhasma(incinerated iron oxide) as one of the main ingredients of anti-anemicherbometallic formulations[25].*ManduraBhasma* (incinerate form of iron-Fe_2O_3), the main component is the activator of the formulation and is the chief responsible component for the pharmacodynamics of *PunarnavaMandura*. By virtue of *Rasa* and *Guna* it pacifies aggravated *Pitha* and maintains the normalcy, improves the digestion and metabolism. Looking in to the diversified actions, *Acharya Charaka* says that, *Mandura* and its preparations are vital in treating cases of *Pandu*. The ferric and ferrous fractions of *Mandura* provide sufficient amount of iron to the living matter, which is needed for normal erythropoiesis [26]. Analytical study of LauhaBhasma and ManduraBhasma revealed the presence of various proportions of important metals along with varied concentration of iron in these. The effect of both the Bhasmas in the management of Pandurogai.e iron deficiency anaemia in animal model as well as human were found to be statistically significant in comparison to the reference standard drug dried ferrous sulphate treatment group. ManduraBhasma was found to be a better haematinic than LauhaBhasma in comparison to reference standard drug [27].

The probable pharmacodynamics according to siddha concept, the ABK is a haematinic synergistic drug showed good effect to increase the haemoglobin level which suggests the ABK possibly increase the Hb by replenishing the IDA. The weakness in IDA due to increase in hypoxia which result in retention of lactic acid whole fatigue developed and decrease work capacity. This is due to imbalance of metabolism (Agni) leading to increase *vatham* and decrease immunity (*ojas*). Improvement of pallor, palpitation and complexion of body manifested by body fluid (*saaram*) and blood (*senner*)dhathus and the function of liver is established well, thus stimulates the circulation and decreases the lactic acid accumulation. The ABK improving digestion and metabolism (*Dhathupakam*) and increases the cardiac function and reduce the cardiac volume, thus the sign palpitation will be reduced. The increase the haematological parameters like Hb,RBC and its indices automatically increase the oxygen supply all over the body while tissue hypoxia reduced thus increase quality of body fluid(*saaram*) due to improved nourishment provide more oxygen to alveolar cells and reduce breathlessness while neuronal function(*vatham*) is established well. It is assumed that the oxygen delivery to the brain and the drug permeates the microchannels(srothas) in the easy way since the nano particle which influence the drug to act on particular recptor (*yokavaki* character of *vatham*), thus decrease headache, memory loss.[28]

4. CONCLUSION

The 102 patients showed statistically significant improvement of subjective parameters like weakness, pallor, palpitation, breathlessness, effort intolerance and pedal odema, thus ABK has proved it is effective in reducing the signs and symptoms of iron deficiency anemia. The

haemoglobin is the most useful and cost effective for assessment of anemic status. In the present study all the cases were examines Hb level in base line, 48th day and 90th day. After treatment with ABK was found to be effective to increase of Hb level and also RBC, PCV, MCV, MCH, MCHC and Serum ferritin level which is the expected results in IDA In the over all, the patients treated with ABK has got relief more than 90% for all the signs and symptoms reported here and well as significant increase in Hb,RBC,PCV,haematological indices and improvement of peripheral blood smear indicate the potency of ABK in reducing symptoms and its haematinic activity. No any treatment related side effect like nausea, vomiting , diarrhoea, constipation ,gastric distress have been reported during the course of study. Hence, ABK can be claimed as safe and effective drug for oral therapy for human at the dose of 1000mg/day for 48 days for the management of IDA.

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Table 1: Socio Demographic Features

Features	Male	Female
No of cases	26	76
Age 19 -40years	13	64
41- 60years	13	12
Civil status - Married	22	38
Un married	04	38
Residence - Rural	14	46
Urban	12	30
Economic status – Low	08	18
Middle	12	48
High	06	10
Dietary Habit - Vegetarian	05	12
Mixed	21	64
Educational Status –Literate	21	69
Ill-literate	05	07

Table 2: symptoms & signs BT & AT

Parameters	No. patients	BT	AT	% of recovery	't' Value	'P' Value (two tailed)
Weakness	102	2.26 ± 0.74	0.04 ± 0.21*	98.23	29.21	0.000
Palpitation	102	1.75 ± 1.09	0.05 ± 0.23*	97.14	16.91	0.000
Pallor	102	1.70 ± 1.01	0.16 ± 0.40*	90.58	14.80	0.000
fatigue	102	1.83 ± 0.97	0.08 ± 0.28*	95.62	17.09	0.000
Breathlessness	102	1.61 ± 1.31	0.05 ± 0.23*	96.89	12.31	0.000
Exercise Intolerance	102	1.33 ± 0.80	0.09 ± 0.29*	93.23	13.81	0.000
Pedal odema	102	0.61 ± 0.74	0.06 ± 0.25*	90.16	7.63	0.000

Values are expressed as Mean ± SD for 102 patients

Figure: 1 symptoms & signs BT & AT

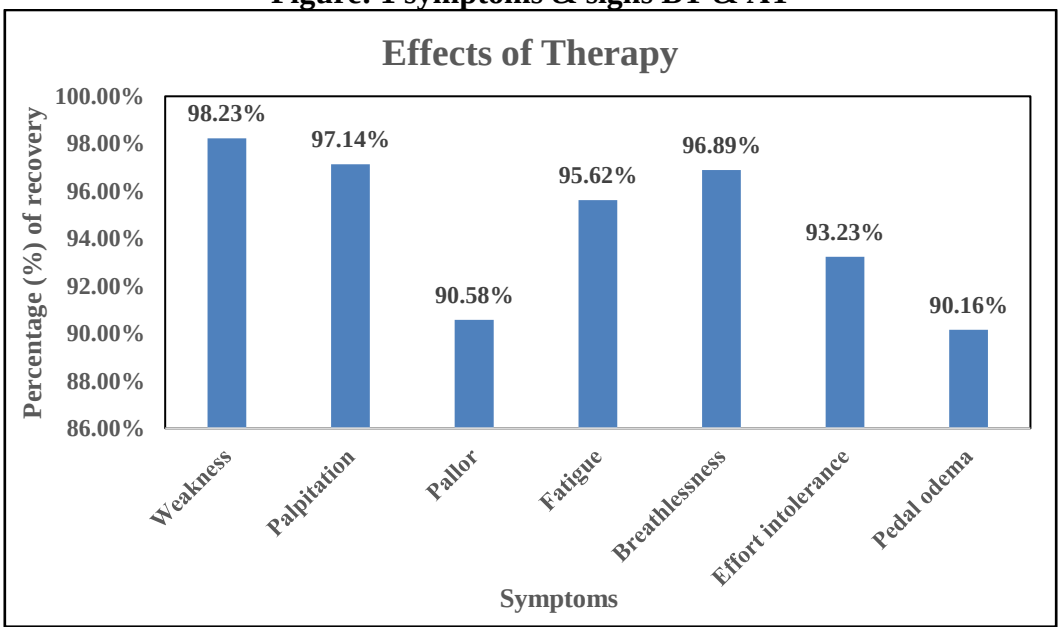

Table.3: Haemoglobin level in clinical model

Parameter	Treatment Group (Day)		
	0 day	**48th Day**	**90th Day**
Hb g/dL	9.31 ± 1.04[a]	11.11 ± 1.00[b]	12.03 ± 1.08[c]

Table.4: Paired Two Sample for Means

Parameters	Treatment group	
	Before treatment (0 Day)	**After treatment (90th Day)**
RBC 10^6uL	4.01 ± 0.40	4.22 ± 0.46*
PCV %	30.79 ± 3.98	36.72 ± 4.91*
MCV fl	76.31 ± 6.80	86.85 ± 7.09*
MCH pg	23.23 ± 2.64	28.58 ± 2.82*
MCHC %	30.28 ± 3.01	33.00 ± 3.28*
Serum Ferritin g/ml	13.81 ± 10.44	92.53 ± 48.79*

- Value expressed as Mean ± SD (n=102)
- **P* value less than alpha 0.05 (P<0.05) for two-tailed test, value was statistically significance compared two treatment group (Before and after treatment group).

Table 5: Peripheral blood smears results

BT.PBS	No of patients	AT. PBS	No of patients	% improvement
MCHC	56	NCNC	50	89.2
MCNC	28	NCNC	23	82.1
NCHC	18	NCNC	10	55.5

Overall improvement 81.37%
No improvement 18.62%